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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
11/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/589,902	WAKITA ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *12-21 and 23-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4 lists*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-26 are pending in the application.

Election/Restrictions

2. Applicant's election with traverse of Group I, and the species wherein the replicon comprises a selectable marker, and wherein the cell is a Huh-7 human liver cell, in the reply filed on October 16, 2008 is acknowledged. The traversal is on the ground(s) that there is an interrelationship among the claimed inventions. This is not found persuasive because while there may be an interrelationship among the inventions, there is no common special technical feature that distinguishes these inventions over the prior art for the reasons indicated in the restriction requirement.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 12-21 and 23-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 16, 2008.

4. Claims 1-11 and 22 are under consideration.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on September 8, 2006; March 27, 2007; and May 16 and August 27, 2008, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements been considered by the examiner.

6. Reference BA in the September 2006 IDS has been considered to the extent of the provided English abstract.

Specification

7. The disclosure is objected to because of the following informalities: the specification indicates on page 14 that SEQ ID NO: 12 is the sequence present in EMBL Accession AB047639 (of record in the August 2008 IDS). However, it is noted that the present SEQ ID NO: 12 includes an additional 24 nucleotides at the 5' terminus, and an additional 5 nucleotides at the 3' end as compared to the EMBL sequence. It is therefore not clear if the statement on page 14 is itself an error; or if the statement, in view of the comparison of the sequences, suggests that there is an error in the provided sequence.

In addition, page 30 of the application indicates that the process for synthesizing RNA used results in an additional 4 3' nucleotides of CUGA. It is noted that the 5 3' nucleotides of SEQ ID NO: 12 additional to the EMBL sequence are CUAGA. It is not clear if this is indicative that the CUAGA sequence is also an artifact of the synthesis process, if the CUAGA sequence in SEQ ID NO: 12 is intended to be CUGA, or if the CUAGA is merely an additional sequence at the 3' terminus of SEQ ID NO: 12 without relation to the discussed CUGA sequence. However, it is noted that the description of SEQ ID NO: 11 indicates that the sequence is not part of the 3' NTR of the HCV 2a genome, and is thus a foreign sequence. The combined teachings indicate that the sequence is a relic of the synthesis process, although it is not clear from the application if the sequence is in fact a mistype for the CUGA sequence of page 30.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim reads as follows:

> A replicon RNA, comprising the following RNA (a) or (b):
>
> (a) an RNA comprising a nucleotide sequence shown in SEQ ID NO: 13; or
>
> (b) an RNA comprising a nucleotide sequence derived from the nucleotide sequence shown in SEQ ID NO: 13 by deletion, substitution or addition of 1 to 100 nucleotides, and having autonomous replication ability and virus particle production ability.

From the claim language, it is not clear if the requirement in part (b) that the RNA has autonomous replication ability and virus particle production ability is intended to apply to both parts ((a) and (b)) of the claim, or if the requirement applies only to subpart (b).

Because the claim is to be read in the broadest reasonable manner, and as the functional claim language appears only in subpart (b) of the claim, and is thus apparently not a requirement for subpart (a), the function is read as applying only to subpart (b) for the purposes of this action.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-11 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

It is also noted that even the presence of multiple species with in a claimed genus does not necessarily demonstrate possession of the genus. See, In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "where there is unpredictability in the performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application."); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support). Thus, when a claim covers a genus of inventions, the specification must provide sufficient written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed, or provided a function and a structure correlating with that function. Moreover, in situations where the operability of other species than

those provided is uncertain, additional support is required over that which would be required where greater certainty is present.

The rejected claims each read on replicon RNAs comprising "A nucleotide sequence shown in" SEQ ID NO: 12 or 13, or the use thereof. In addition, the claims each require that the replicon has "autonomous replication ability and virus particle production ability" or confers upon a cell into which it is delivered the ability to replicate RNA and produce a viral particle.

It is noted that these claims vary from the requirements of claim 1 in two respects. First, claim 1 is limited to replicons comprising the indicated regions "of genomic RNA of hepatitis C virus of genotype 2a." I.e. the claim requires the use of unaltered coding and NTR regions from an HCV genotype 2a viral genome. The presently rejected claims require only that the replicons comprise a sequence from SEQ ID NO: 12 or 13. They do not require that the sequence comprises each of the regions of the HCV genome, or that the included regions are unaltered as compared to an isolated HCV 2a viral genome, so long as a portion of the sequence of SEQ ID NO: 12 or 13 is present.

In support of the claimed invention, the present application teaches an HCV genotype 2a full length replicon, and provides examples of a limited number of mutant forms thereof. However, the application does not disclose what structures or sequences correlate with the operability of HCV replicons in general, either for replication or for the production of viral particles. Nor, does the application provide any examples of replicons of other genotypes of HCV.

Other teachings in the art have provided examples of HCV replicons that are capable of replication. See e.g., Ikeda et al., J Virol 76: 2997-3006 (of record in the September 2006 IDS).

However, the art also teaches that the construction of HCV replicons for other HCV genotypes have not been successful. See e.g., Ikeda, at 2998 (left column). In fact, those in the art have been unable to make operable replicons even from other HCV 2a genomes. See e.g., Date et al., Hepatol Res 37:433-43, at 439 (teaching that replicons of HCV genotype 2a strain J6CF did not replicate in tissue culture); and Meunier et al., PNAS 102:4560-65, at 4561-62 (teaching that HCV strain J6CF is a genotype 2a HCV virus). Thus, the teachings in the art indicate that there is uncertainty in the operability of HCV sequences to produce operable replicons as claimed. The teachings indicate that this uncertainty extends even to different viral genome sequences within the HCV genotype 2a.

Moreover, because the art indicates that even intra-genotypic sequence variations may result in rendering a replicon in-operable, the teachings also implicitly indicate that effects of making mutations to such sequences would also be uncertain. Thus, the teachings in the art indicate that there is uncertainty in the operability of other sequences that those disclosed to form an operable replicon.

This uncertainty is even more significant with respect to the functional limitations of claims 5-10 and 22, which read not only on replicons, but on replicons (and cells comprising such) that are additionally capable of producing viral particles. The teachings in the art indicate that, even with other full-length replicons that have been shown to replicate in cells, the replicons do not appear to produce viral particles. See e.g., Pietschmann et al., J Virol 76:4008-21, abstract, page 4019. Rather, the only replicons that have been shown to produce viral particles appear to be those comprising the non-structural protein coding region of the JFH-1 strain, the strain represented by SEQ ID NOs: 1-13 of the present application. See e.g., Mateu et al.,

Virology 376:397-407; and Gottwein et al., Gastroenterol 133:1614-26. In view of these teachings, it is apparent that there is even greater uncertainty as to what operable replicons would be capable of producing viral particles, and what mutations may be made to the non-structural regions of the JFH1 coding regions without a loss of this apparently unique functional characteristic.

In view of the limited numbers of examples provided by the application, the teachings in the art demonstrating uncertainty both in what other HCV strains and genotypes have genomic sequences that may be used to produce operable replicons, and as to what other modifications may be made to the replicon of SEQ ID NO: 13 so as to retain functionality, the claims are rejected as lacing adequate descriptive support for the full scope of the claimed genus.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Kato et al. (Gastroenterol 128:1808-17- of record in the March 2007 IDS). This claim is directed to "[a] replicon RNA, comprising the following RNA (a) or (b):

(a) an RNA comprising a nucleotide sequence shown in SEQ ID NO: 13…"

It is noted that the claim does not require that the replicon RNA comprises the full sequence of SEQ ID NO: 13. Nor does the claim require that the replicon RNA encodes the full-length HCV 2a polyprotein. The claim therefore reads on a subgenomic replicon of HCV.

Kato teaches a subgenomic replicon of HCV 2a. Abstract. The sequence of the replicon identified as pSGR-JFH1 is provided in GenBank Accession AB114136. A comparison of this sequence with SEQ ID NO: 13 shows that numerous sequences found in SEQ ID NO: 13 are also found in the replicon of Kato. The reference therefore anticipates the claim.

14. Claims 5 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Blanchard et al. (J Virology, 76:4073-79). These claims have been described above. Blanchard teaches an RNA replicon that autonomously replicates, and produces a virus-like particle. Abstract. The replicon is disclosed as the pSFV1 replicon, a portion of the sequence of which is provided (using DNA sequence) in Ciccarone et al. (Focus 15:103-105, at 104, Figure 2). As can be seen, the promoter region of the replicon includes sequences found in SEQ ID NO: 13, including the sequences "acc" and “ggcgg" (see e.g., residues 1-3 and 1034-1038 of SEQ ID NO: 13). Because the claims do not specify the type of viral particles to be produced, or require the presence of the full-length of SEQ ID NO: 12 or 13 or set a minimum length of the sequences from these sequence to be present in the replicons, the Blanchard reference anticipates the indicated claims.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-11 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kato et al. (Gastroenterol 128:1808-17- supra) in view of Ikeda et al. (J Virol 76:2997-3006-of record in the September 2006 IDS) and of EMBL AB047639 (of record in the August 2008 IDS). These claims are drawn to HCV 2a replicons comprising the nucleic acid sequences encoding the full-length HCV polyprotein; and to cells transfected, and methods of transfecting cells, with the replicons. Claims 3-5 and 22 require that the replicon comprises a sequence from at least one of SEQ ID NOs: 1-13. Claims 5, 6-10, and 22 require that the replicon or transfected cell, replicates the RNA, and produces a viral particle.

Kato teaches HCV 2a subgenomic replicons. In one instance, the replicon is pSGR-JFH1, which includes sequences found in each of SEQ ID NOs: 1 and 5-13. Page 1809. See also, GenBank AB114136 (teaching the sequence of the replicon). The reference also teaches the transfection of the replicons in to Huh-7 cells. However, the reference teaches a subgenomic replicon, which does not include Core, E1, or E2 encoding sequences, and therefore does not produce a viral particle. The Kato replicon varies from SEQ ID NO: 13 in lacking the coding sequences for these HCV 2a proteins.

However, the teachings of Ikeda indicate that full-length HCV replicons would have been recognized by those of ordinary skill in the art as functional equivalents of subgenomic replicons. See e.g., abstract. Moreover, the sequence of the HCV genome from which the replicons of SEQ ID NO: 13 and of Kato were made was also known in the art. See, EMBL AB047639. It would therefore have been obvious to those of ordinary skill in the art to have

added the structural protein sequences from the EMBL sequence into the subgenomic replicon of Kato to have made a replicon encoding the full-length HCV 2a genome. By constructing the full-length replicon, and transfecting such in to cells, those in the art would have made replicons and cells meeting the functional limitations of claims 3-5 and 22. The combined teachings of the cited references therefore render the claimed inventions obvious.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 1-5 and 22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 and 21 of copending Application No. 10/558155 in view of Ikeda et al. (supra). The present claims differ from the claims of the copending application in that the copending application is silent as the presence of the structural protein. However, as was indicated above, present claim 5 does not require that the replicon is a full length replicon. Thus, the copending claims would anticipate that claim if applied as prior art.

With respect to the remaining claims of the present application, it is noted that SEQ ID NO: 3 of the copending application (referenced in copending claim 4). Moreover, the copending claims do not exclude the presence of the additional HCV protein coding sequences. Further, as was described above, the teachings of Ikeda indicate that full-length HCV replicons are functional equivalents of the subgenomic replicons consisting of the proteins identified in the copending claims. From these teachings, it would have been obvious to those of ordinary skill in the art to have included the structural protein coding sequences of SEQ ID NO: 3 of the copending application in the replicons of the copending claims, thereby resulting in the replicons of the present claims. The present claims therefore represent obvious embodiments of the copending claims.

This is a provisional obviousness-type double patenting rejection.

20. Claim 5 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-8 of copending Application No. 11/898468, and over claim 34 of copending application 10/572,476. Although the conflicting claims are not identical, they are not patentably distinct from each other because, as indicated above, claim 5 reads on a replicon, including subgenomic replicons, that comprise a sequence found within SEQ ID NO: 13.

The copending claims of the '468 application read on replicons comprising the sequences of SEQ ID NOs: 2, 5, and 6 of that application, of which at least SEQ ID NO: 2 shares common sequences with present SEQ ID NO: 13. See, alignment of SEQ ID NO: 12 (representing the HCV genome included in SEQ ID NO: 13) and copending SEQ ID NO: 2.

It is noted that the SEQ ID NO: 7 referenced in '476 application includes the sequence of the '468 application SEQ ID NO: 2. Thus, the claims of that application also share sequences with SEQ ID NO: 13.

The copending claims would therefore anticipate the present claims if applicable as prior art, making the obviousness type double patenting rejection appropriate.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is (571)272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachariah Lucas/
Primary Examiner, Art Unit 1648